

**WHAT IS CLAIMED IS:**

1. An isolated polypeptide having protease activity for a specific protease cleavage site, wherein the protease activity is specific for a substrate peptide having an amino acid sequence comprising:



wherein  $R_1$  and  $R_3$  are independently any D or L isomer amino acid,  $R_2$  is Ala or Gly, and wherein the specific protease cleavage site is between Asp and  $R_2$ .

2. The isolated polypeptide of claim 1 wherein the substrate peptide is at least eight amino acids in length.

3. An isolated IL-1 $\beta$  pro polypeptide having IL-1 $\beta$  pro activity and encoded by a DNA sequence comprising:

a. a DNA insert selected from the group consisting of the nucleotide sequences in Seq. I.D. No. 1 beginning at nucleotide 1 and extending to nucleotide 1232, beginning at nucleotide 374 and extending to nucleotide 1232, and beginning at nucleotide 374 and extending to a nucleotide from about 851 to about 962,

b. DNA sequences which detectably hybridize to one or more of the foregoing DNA inserts and which code or express a polypeptide displaying biological activity to proteolytically cleave human precursor IL-1 $\beta$  polypeptide at a cleavage site between the Asp 116 and Ala 117 residues; and

c. DNA sequences which, due to degeneracy of the genetic code, encode a mammalian IL-1 $\beta$  pro polypeptide encoded by any of the foregoing DNA inserts and sequences.

4. The isolated polypeptide of claim 3 wherein the protein sequence is selected from the group consisting of amino acid 1 to amino acid 404, amino acid 51 to amino acid 404, amino acid 120 to an amino acid beginning at position 278 and extending to amino acid 315, and amino acid 120 to amino acid 404 of Seq. I.D. No. 2.

5. An isolated DNA sequence encoding a mammalian IL-1 $\beta$  pro enzyme.

6. The isolated DNA sequence of claim 5 wherein the mammalian IL-1 $\beta$  pro enzyme is a human IL-1 $\beta$  pro enzyme.

7. The isolated DNA sequence of claim 5 wherein the DNA sequence comprises:

a. a DNA insert selected from the group consisting of the nucleotide sequences in Seq. I.D. No. 1 beginning at nucleotide 1 and extending to nucleotide 1232, beginning at nucleotide 374 and extending to nucleotide 1232, beginning at nucleotide 374 and extending to a nucleotide from about 851 to about 962;

b. DNA sequences which detectably hybridize to one or more of the foregoing DNA inserts and which code or express a polypeptide displaying biological activity to proteolytically cleave human precursor IL-1 $\beta$  polypeptide at a cleavage site between the Asp 116 and Ala 117 residues; and

c. DNA sequences which, due to degeneracy of the genetic code, encode a mammalian IL-1 $\beta$  pro polypeptide encoded by any of the foregoing DNA inserts and sequences.

8. A recombinant expression vector comprising a DNA sequence according to claim 5.

9. A recombinant expression vector comprising a DNA sequence according to claim 6.

10. A recombinant expression vector comprising a DNA sequence according to claim 7.

11. A process for preparing a mammalian IL-1 $\beta$  pro enzyme or an analog or derivative thereof, comprising culturing a suitable host cell comprising a vector according to claim 8 under conditions promoting expression.

12. A process for preparing a mammalian IL-1 $\beta$  pro enzyme or an analog or derivative thereof, comprising culturing a suitable host cell comprising a vector according to claim 9 under conditions promoting expression.

13. A process for preparing a mammalian IL-1 $\beta$  pro enzyme or an analog or derivative thereof, comprising culturing a suitable host cell comprising a vector according to claim 10 under conditions promoting expression.

14. A method for improving wound healing at a wound site comprising administering a pharmaceutical composition to the wound site comprising the isolated polypeptide of claim 1 in a suitable pharmaceutical carrier.

15. A method for treating arthritis comprising administering a pharmaceutical composition

comprising the isolated polypeptide of claim 1 in a suitable pharmaceutical carrier.

16. A method for treating an autoimmune disease in a susceptible individual comprising administering a pharmaceutical composition comprising the isolated polypeptide of claim 1 in a suitable pharmaceutical carrier.

17. The method of claim 16 wherein the autoimmune disease is selected from the group consisting of Insulin-dependent diabetes melitus, Graves' disease, Hashimotos disease and a lupus disease.

18. A method for reducing the detrimental side effects of radiation treatment comprising administering a pharmaceutical composition comprising the isolated polypeptide of claim 1 in a suitable pharmaceutical carrier.

19. An antisense oligonucleotide comprising a sequence of at least 15 nucleotides complementary to a sequence of IL-1 $\beta$  pro cDNA, wherein said antisense oligonucleotide inhibits translation of IL-1 $\beta$  pro mRNA.

20. A compound comprising an amino acid sequence of from 1 to about 5 amino acid residues having an N-terminal blocking group and a C-terminal Asp residue connected to an electronegative leaving group, wherein said amino acid sequence substantially corresponds to at least a portion of the sequence Ala-Tyr-Val-His-Asp, residues 112 to 116 of Seq. I.D. No. 3.

112 R2

21. The compound according to claim 20 having the formula:

Sub Q2

*Sub A<sup>3</sup>*  
Contd

Z-Q<sub>2</sub>-Asp-Q<sub>1</sub>

where Z is an N-terminal protecting group;  
Q<sub>2</sub> is 0 to 4 amino acids such that the sequence Q<sub>2</sub>-Asp  
substantially corresponds to at least a portion of the  
sequence Ala-Tyr-Val-His-Asp, residues 112 to 116 of  
Seq. I.D. No. 3; and  
Q<sub>1</sub> is an electronegative leaving group:

22. The compound according to claim 21  
wherein Z is C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl, acetyl, C<sub>1</sub>-C<sub>6</sub>  
alkoxycarbonyl, benzyloxycarbonyl or C<sub>1</sub>-C<sub>6</sub> alkyl  
carbonyl.

23. The compound according to claim 21  
wherein Z is t-butoxycarbonyl, acetyl or  
benzyloxycarbonyl.

24. The compound according to claim 21  
wherein Q<sub>1</sub> is an aldehyde, a diazomethyl ketone or a  
halomethyl ketone.

25. The compound according to claim 21  
wherein Q<sub>1</sub> is fluoromethyl ketone.

26. The compound according to claim 21  
wherein Q<sub>2</sub> is 1 amino acid residue.

27. The compound according to claim 21  
wherein Q<sub>2</sub> is His, Phe, Pro or Tyr.

28. A pharmaceutical composition comprising a  
physiologically acceptable carrier and a compound of the  
formula:

A-Q<sub>2</sub>-Asp-Q<sub>1</sub>

where Z is an N-terminal protecting group;

Sub A<sup>3</sup>

*Sub A. 3  
Contd*

$Q_2$  is 0 to 4 amino acids such that  $Q_2$ -Asp substantially corresponds to at least a portion of the sequence Ala-Tyr-Val-His-Asp, residues 112 to 116 of Seq. I.D. No. 3; and

$Q_1$  is an electronegative leaving group:

29. The composition according to claim 28 wherein Z is  $C_1-C_6$  alkyl, benzyl, acetyl,  $C_1-C_6$  alkoxy carbonyl, benzyloxycarbonyl or  $C_1-C_6$  alkoxy carbonyl, benzyloxycarbonyl or  $C_1-C_6$  alkyl carbonyl.

30. The composition according to claim 28 wherein Z is t-butoxycarbonyl, acetyl or benzyloxycarbonyl.

31. The composition according to claim 28 wherein  $Q_1$  is an aldehyde, a diazomethyl ketone or a halomethyl ketone.

32. The composition according to claim 28 wherein  $Q_1$  is fluoromethyl ketone.

33. The composition according to claim 28 wherein  $Q_2$  is 1 amino acid residue.

34. The composition according to claim 28 wherein  $Q_2$  is His, Phe, Pro or Tyr.

35. A method of inhibiting IL-1 $\beta$  protease activity in a mammal in need of such treatment comprising administering to said mammal an effective inhibitory amount of a compound of the formula:



where Z is an N-terminal protecting group;

$Q_2$  is 0 to 4 amino acids such that the sequence  $Q_2$ -Asp substantially corresponds to at least a portion of the sequence Ala-Tyr-Val-His-Asp, residues 112 to 116 of Seq. I.D. No. 3; and

$Q_1$  is an electronegative leaving group.

36. The method according to claim 35 wherein  $Z$  is  $C_1-C_6$  alkyl, benzyl, acetyl,  $C_1-C_6$  alkoxy carbonyl, benzyloxycarbonyl or  $C_1-C_6$  alkyl carbonyl.

37. The method according to claim 35 wherein  $Z$  is t-butoxycarbonyl, acetyl or benzyloxycarbonyl.

38. The method according to claim 35 wherein  $Q_1$  is an aldehyde, a diazomethyl ketone or a halomethyl ketone.

39. The method according to claim 35 wherein  $Q_2$  is 1 amino acid residue.

40. The method according to claim 35 wherein  $Q_2$  is His, Phe, Pro or Tyr.

41. The method according to claim 35 wherein  $Q_1$  is an aldehyde and inhibiting is reversibly inhibiting.

42. The method according to claim 35 wherein  $Q_1$  is fluoromethyl ketone and inhibiting is irreversibly inhibiting.

43. A method of treating inflammation or preventing and treating an autoimmune disease in a mammal instead of such treatment comprising administering to said mammal an effective amount of a compound of the formula:

*Sub A*

*Sub A  
cont'd*

Z-Q<sub>2</sub>-Asp-Q<sub>1</sub>

where Z is an N-terminal protecting group;  
Q<sub>2</sub> is 0 to 4 amino acids such that the sequence Q<sub>2</sub>-Asp substantially corresponds to at least a portion of the sequence Ala-Tyr-Val-His-Asp, residues 112 to 116 of Seq. I.D. No. 3; and  
Q<sub>1</sub> is an electronegative leaving group:

44. The method according to claim 43 wherein Z is C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl, acetyl, C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl.

45. The method according to claim 43 wherein Z is t-butoxycarbonyl, acetyl or benzyloxycarbonyl.

46. The method according to claim 43 wherein Q<sub>1</sub> is an aldehyde, a diazomethyl ketone or a halomethyl ketone.

47. The method according to claim 43 wherein Q<sub>2</sub> is 1 amino acid residue.

48. The method according to claim 43 wherein Q<sub>2</sub> is His, Phe, Pro or Tyr.

49. A compound selected from the group consisting of Boc-Asp-CF<sub>2</sub>F, Boc-His-Asp-CH<sub>2</sub>F, Boc-Phe-Asp-CH<sub>2</sub>F, Boc-Pro-Asp-CH<sub>2</sub>F, Boc-Tyr-Asp-CH<sub>2</sub>F, Ac-His-Asp-CH<sub>2</sub>F, Ac-Phe-Asp-CH<sub>2</sub>F, Ac-Pro-Asp-CH<sub>2</sub>F, Ac-Tyr-Asp-CH<sub>2</sub>F, Cb<sub>3</sub>-His-Asp-CH<sub>2</sub>F, Cb<sub>3</sub>-Phe-Asp-CH<sub>2</sub>F, Cb<sub>3</sub>-Pro-Asp-CH<sub>2</sub>F, and Cb<sub>3</sub>-Tyr-Asp-CH<sub>2</sub>F wherein Boc is t-butoxycarbonyl, Ac is acetyl and Cb<sub>3</sub> is benzyloxycarbonyl.